EXTENDED REPORT

Efficacy of sulfasalazine in patients with inflammatory back pain due to undifferentiated spondyloarthritis and early ankylosing spondylitis: a multicentre randomised controlled trial

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Ann Rheum Dis 2006;**65**:1147–1153. doi: 10.1136/ard.2006.052878

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Accepted 4 April 2006
Published Online First 10 April 2006

Objectives: To assess the effect of sulfasalazine (SSZ) on inflammatory back pain (IBP) due to active undifferentiated spondyloarthritis (uSpA) or ankylosing spondylitis in patients with symptom duration <5 years.

Methods: Patients with IBP and a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) >3 from 12 centres were randomly assigned to 24 weeks' treatment with SSZ 2 g/day or placebo. The primary outcome variable was the change in BASDAI over 6 months. Secondary outcomes included measures of spinal pain, physical function and inflammation.

Results: 230 patients (50% men, age range 18–64 years, 67% human leucocyte antigen B27 positive) were treated with either SSZ 2×1 g/day or placebo for 6 months. Enthesitis was found in 50%, and peripheral arthritis in 47% of the patients. The mean (SD) BASDAI dropped markedly in both groups: by 3.7 (2.7) and 3.8 (2.4), respectively, as did most secondary outcome measures. No noticeable difference in treatment was observed between groups. Patients with IBP and no peripheral arthritis had significantly ($p=0.03$) more benefit with SSZ (BASDAI 5.1 (1.3) to 2.8 (2.3)) than with placebo (5.2 (1.6) to 3.8 (2.4)). Spinal pain ($p=0.03$) and morning stiffness ($p=0.05$) improved with SSZ in these patients, but other secondary outcomes were not markedly different.

Conclusion: SSZ was no better than placebo for the treatment of the signs and symptoms of uSpA; however, SSZ was more effective than placebo in the subgroup of patients with IBP and no peripheral arthritis.

The spondyloarthritides, including ankylosing spondylitis, are characterised by inflammatory back pain (IBP), sacroiliitis, peripheral arthritis, enthesitis and morning stiffness, together with an association with human leucocyte antigen (HLA) B27 and familial predisposition. The European Spondyloarthropathy Study Group (ESSG) classification criteria[1] are widely used to diagnose spondyloarthritis (SpA), and different subtypes are recognised according to clinical features, including ankylosing spondylitis, psoriatic SpA, inflammatory bowel disease-associated SpA and reactive SpA. Undifferentiated SpA (uSpA) is a diagnosis of exclusion, and can include patients with IBP who may have early ankylosing spondylitis but do not yet fulfil the modified New York criteria for ankylosing spondylitis.[2] More than half of the patients with uSpA will develop ankylosing spondylitis over time.[3]

Sulfasalazine (SSZ), a well-established disease-modifying antirheumatic drug (DMARD), is the only DMARD that is useful for any of the clinical manifestations of SpA, such as ankylosing spondylitis. It is effective in the peripheral arthritis associated with SpA,[4 5] and a recent Cochrane review on SSZ in ankylosing spondylitis showed marked improvement in inflammatory indices, including morning stiffness and erythrocyte sedimentation rate (ESR), with treatment.[6] SSZ may therefore be beneficial to patients with early, active disease and peripheral arthritis. However, the influence of DMARDs such as SSZ on early spinal manifestations of SpA has not been studied to date.

This study was designed to investigate whether treatment with SSZ at 2×500 mg twice daily over 6 months is effective in patients with IBP due to active uSpA and early ankylosing spondylitis.

PATIENTS AND METHODS

Patients

Adult patients with IBP and SpA according to the ESSG criteria[1] were eligible for the study. Only patients with IBP symptom duration between 3 months and 5 years and active disease as defined by a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)[7] score of >3 were included. A patient is classified as having SpA by the ESSG criteria if one of the two entry criteria (IBP or predominantly lower-limb synovitis) and one other feature of SpA are present. Patients were included if they had an associated family history of SpA, alternating buttock pain, enthesopathy or sacroiliitis. Patients with associated inflammatory bowel disease, psoriasis, a preceding symptomatic infection of the urogenital or enteral tract in the 4 weeks before the onset of symptoms or

Abbreviations: BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; DMARD, disease-modifying antirheumatic drug; ESR, erythrocyte sedimentation rate; ESSG, European Spondyloarthropathy Study Group; HLA, human leucocyte antigen; IBP, inflammatory back pain; NSAID, non-steroidal anti-inflammatory drug; SpA, spondyloarthritis; SSZ, sulfasalazine; uSpA, undifferentiated spondyloarthritis; WOMAC, Western Ontario and MacMaster

Table 1 Baseline characteristics and clinical characteristics of the study population

Characteristics	SSZ (n = 120)	Placebo* (n = 122)
Men (%)	57 (47.5)	60 (49.2)
Mean (SD) age (years)	38.3 (11.4)	38.8 (11.9)
HLA B27 positive (%)	76/111 (63.3)	77/118 (63.1)
Peripheral arthritis (%)	57 (47.5)	57 (46.7)
Mean (SD) number of swollen joints (range 0–68), at baseline (in patients with peripheral arthritis)	5.5 (4.5), n = 52	6.1 (4.7), n = 54
Enthesitis (%)	65 (54.2)	58 (47.5)
Mean (SD) number of enthesitic regions (range 0–12) at baseline (in patients with enthesitis)	4.3 (3.2), n = 60	4.1 (2.8), n = 55
Current occurrence or history of anterior uveitis (%)	3 (2.5%)	4 (3.3%)

HLA, human leucocyte antigen; SSZ, sulfasalazine.
*Not significantly different from the group receiving SSZ, all p>0.2.

ankylosing spondylitis with ankylosis (more than one syndesmophyte on spinal radiograph)—that is, specific SpA diagnoses—were excluded. Also excluded were pregnant women and patients with current severe renal or hepatic disease or hypersensitivity to drugs structurally similar to sulfonamides or salicylates. The included patients were therefore classified as having uSpA (fulfilling ESSG criteria, but not fulfilling the diagnoses of inflammatory bowel disease-associated SpA, psoriatic arthritis or reactive arthritis) or early ankylosing spondylitis, without evidence of spinal ankylosis.

When available, radiographs of sacroiliac joints, the cervical spine and lumbar spine were scored by one reader (XB) trained in radiological scoring of ankylosing spondylitis.

Patients were allowed to receive any concurrent non-steroidal anti-inflammatory drugs (NSAIDs) and the dose was recorded. The NSAID dosage could be decreased but not increased. Other DMARDs and oral corticosteroids were not permitted, and, if present, were withdrawn 4 weeks before screening.

The study was conducted in 12 European centres. The study protocol was reviewed and approved by the respective institutional review board or independent ethics committee at each site. All patients gave written informed consent.

Study protocol

In this 24-week, multicentre, randomised, double-blind, placebo-controlled trial, patients were randomly assigned to receive SSZ or placebo twice daily. Patients were allocated to treatment groups without stratification, by a central randomisation office. Patients, investigators and outcome assessors were blinded to treatment allocation. The study drug was distributed by the local pharmacist at each site.

Study drug

Patients received an initial dose of 500 mg study drug, which was increased weekly by 500 mg to at least 2×500 mg twice daily. SSZ and matching placebo were provided by Pharmacia & Upjohn (Karlsruhe, Germany). The dosage of 2 g per day was chosen on the basis of previous experience with SSZ for ankylosing spondylitis and SpA.[4 5]

Efficacy evaluations

The primary end point of the study was improvement in disease activity at week 24 as measured by the BASDAI, which is based on six questions relating to fatigue, spinal pain, peripheral arthritis, enthesitis and morning stiffness.

Secondary outcome parameters included improvements in spinal pain and inflammation as measured by questions of the BASDAI, physical function as measured by the Bath Ankylosing Spondylitis Functional Index (BASFI[8]) and the Western Ontario and MacMaster Universities Osteoarthritis Index (WOMAC[9]); improvement in spinal mobility as measured by Schober's test and chest expansion; and reduction in inflammatory activity as indicated by a 68-joint swollen joint count, the Berlin Enthesitis Index assessing 12 enthesitic regions,[10] CRP and ESR. Pain and morning stiffness were assessed using the pain and stiffness items from the WOMAC Index. At baseline and at each monthly clinical visit, the full blood count, leucocyte and differential count, ESR, C reactive protein and biochemical profiles of sodium, potassium, calcium, creatinine and liver were measured, and consumption of NSAIDs and any occurrence of uveitis was recorded. The validated questionnaires (BASDAI, BASFI and WOMAC Index) were administered, and joint and entheseal counts were taken at weeks 0, 8, 16 and 24. Data on NSAID intake were collected at each interview and converted to a ''diclofenac equivalent dosage'' to permit comparisons.[11]

Radiographic evaluation included assessment of the radiographs of the vertebral column and the sacroiliac joints in the presence of appropriate clinical symptoms at baseline. Radiographs not older than 6 months were considered to be sufficient.

Safety evaluations

Safety assessments were carried out at each monthly clinical visit to assess any suspected adverse drug reactions, reactions from drug overdose, withdrawal or sensitivity, deterioration of SpA, defined as inflammation of a new joint or a new extraskeletal manifestation, abnormalities in physiological testing and laboratory abnormalities.

Statistical analysis

The sample size was calculated to detect a difference in the BASDAI of 0.6 points (mean change in score 0.52) between the groups, with a power of 80%, $\alpha = 0.05$ and a standard deviation (SD) of 1.4, based on unpublished data from one of our earlier studies. Allowing for an expected withdrawal rate of 15%, a minimum of 100 patients was therefore required in each arm. The main analysis was based on an intention-to-treat approach, using the carry-forward principle for missing data. All tests were based on a two-sided test procedure with 95% confidence intervals, without adjustment for multiple testing. The distribution of all continuous variables was evaluated using the Kolmogorow–Smirnov test. Normal or symmetrical distributions were compared using the independent samples t test, the paired t test or repeated measures analysis. Non-parametric data were compared using the Mann–Whitney–Wilcoxon test. Categorical variables were evaluated using the χ^2 test.

RESULTS

Data were collected between May 2000 and July 2003. In all, 242 patients were randomly assigned to treatment with placebo (n = 120) or SSZ (122 patients). There were no statistically significant differences between the two groups at baseline (table 1). The study population had similar numbers of men and women (117/242 men, 48.4%) with a mean age of 38 (range 18–64) years; 67% (153/229) were HLA B27 positive. All patients had a disease duration of <5 years (as per protocol). In all, 91% reported pain in the lumbar spine, 39% had symptoms in the thoracic spine and 33% in the cervical spine. In addition to IBP, 50% of the patients had enthesitis, 47% peripheral arthritis, 14% dactylitis and 3% had uveitis. The CRP level was strongly raised (>10 mg/dl) in

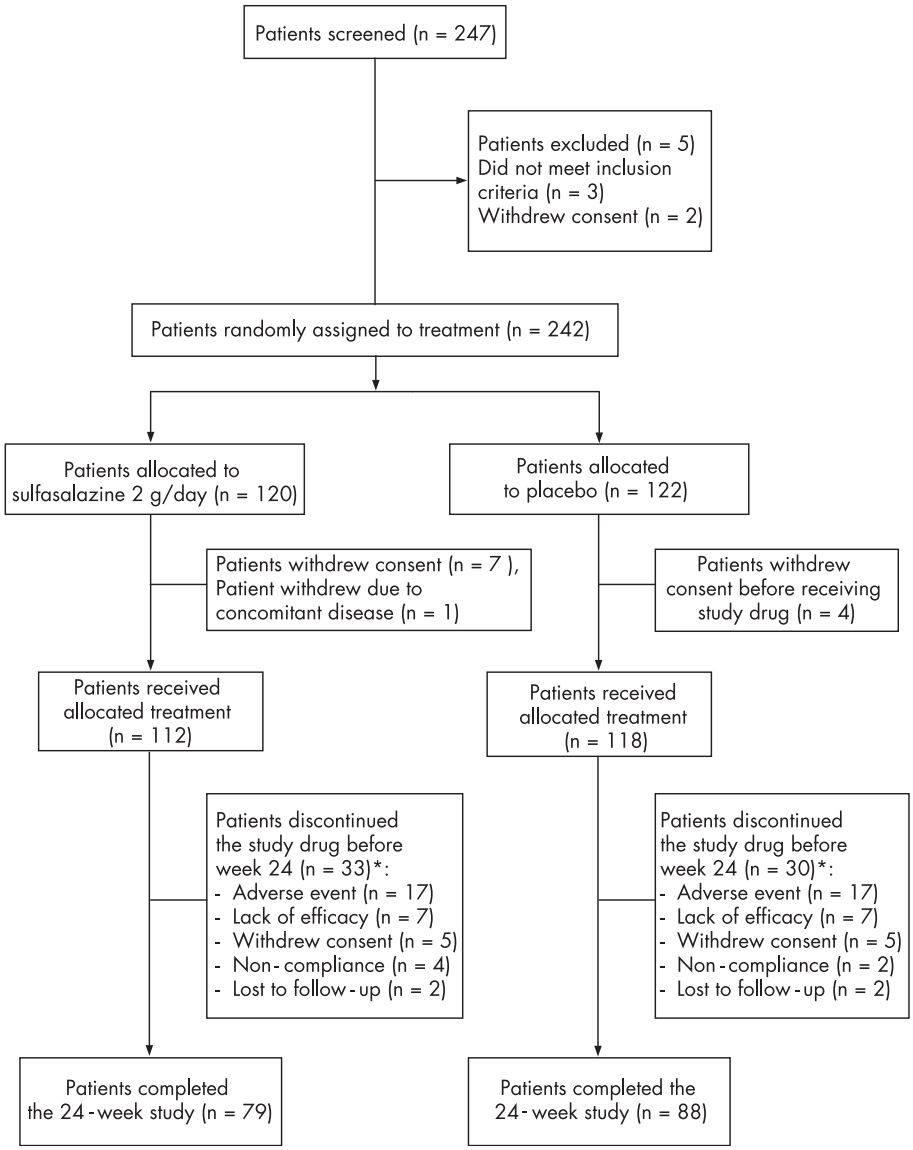

Figure 1 Patient progression through the phases of the trial. *More than one reason for withdrawal was given for some patients.

31% and moderately raised (1–10 mg/dl) in 49% of the patients; 20% had normal CRP levels.

Radiographs of the sacroiliac joint were available for 90 patients, cervical spine radiographs for 35 patients and lumbar spine radiographs for 75 patients. A trained reader (XB) identified 12 patients with sacroiliac joint changes consistent with ankylosing spondylitis and eight with early syndesmophytes on spinal radiographs (not identified by the initial referring clinicians). Only two patients had both sacroiliac joint and spinal changes of ankylosing spondylitis on imaging. Extrapolating these findings, it may be assumed that 13% (12/90) of the total cohort showed radiographic changes fulfilling the modified New York criteria for ankylosing spondylitis. Patients who fulfilled the radiological criteria for ankylosing spondylitis were not excluded from the analysis; this did not markedly change the results. We found no major differences in clinical parameters between those patients who had radiographs and those who did not.

Eight patients randomised to the SSZ arm and four patients in the placebo arm did not receive any intervention (11 withdrew consent and one withdrew due to concomitant disease) and so have not been included in the analysis. The mean age of those who withdrew was 41.4 years and 75% were women. Excluding these patients did not markedly change the characteristics of either treatment group. In total, 112 patients were treated with SSZ 2×1 g per day and 118 were treated with placebo for up to 6 months.

The two groups showed no significant differences regarding sex, HLA B27, clinical features, radiographic changes of the spine and acute-phase parameters. The mean (SD) BASDAI was comparable in the two groups (5.5 (1.6) in the SSZ group *v* 5.4 (1.6) in the placebo group; $p = 0.40$). We found no difference in mean BASFI between groups (mean BASFI was 3.6 (2.4) in the SSZ group *v* 3.3 (2.0) in the placebo group; $p = 0.37$).

Patients with and without peripheral arthritis did not differ significantly with regard to sex ($p = 0.59$), HLA B27 ($p = 0.38$) or age ($p > 0.20$). Of patients randomised to treatment with SSZ, those with peripheral arthritis had a significantly higher BASDAI than those with axial symptoms alone (5.93 *v* 5.07; $p = 0.004$), and as expected, patients with peripheral arthritis in both SSZ and placebo groups had higher scores for peripheral joint pain (question 3 of BASDAI) than those without peripheral arthritis ($p < 0.01$

Table 2 Effect of treatment on clinical and biological outcomes at week 24

	SSZ (n = 112)		Placebo (n = 118)			
	Mean (SD) at baseline	Mean (SD) change at week 24	Mean (SD) at baseline	Mean (SD) change at week 24	Mean difference (95% CI)	p Value
BASDAI score (0–10)	5.54 (1.59)	−1.76 (0.20)	5.37 (1.57)	−1.52 (0.21)	−0.24 (−0.82 to 0.33)	0.407
BASFI score (0–10)	3.57 (2.42)	−0.46 (0.17)	3.32 (1.98)	−0.28 (0.19)	−0.18 (−0.67 to 0.31)	0.474
WOMAC Index, pain	3.58 (2.78)	−0.48 (0.26)	3.31 (2.46)	−0.49 (0.23)	0.01 (−0.62 to 0.64)	0.974
WOMAC Index, stiffness	3.86 (3.12)	−0.63 (0.27)	3.85 (2.93)	−0.71 (0.27)	0.08 (−0.66 to 0.83)	0.819
WOMAC Index, physical function	3.33 (2.70)	−0.45 (0.19)	3.02 (2.28)	−0.27 (0.17)	−0.18 (−0.68 to 0.31)	0.464
Schober's test (cm)	3.44 (1.13)	0.19 (0.12)	3.57 (1.06)	0.26 (0.13)	−0.06 (−0.40 to 0.28)	0.717
Chest expansion (cm)	3.92 (1.67)	0.07 (0.14)	3.96 (1.62)	0.14 (0.15)	−0.07 (−0.49 to 0.34)	0.751
CRP (mg/dl) in patients with raised CRP >10 mg/dl at baseline	20.25 (10.91), n = 35	−3.05 (13.63)	24.10 (16.35), n = 25	−7.84 (16.94)	4.78 (−3.13 to 12.69)	0.232
ESR (mm at the end of the first hour) in patients with raised ESR>15 mm at the end of the first hour at baseline	27.48 (12.64), n = 48	−9.25 (16.80)	29.40 (16.58), n = 43	−7.02 (15.53)	−2.23 (−8.99 to 4.54)	0.515

BASDAI, Bath Ankylosing Spondylitis Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; CRP, C reactive protein; ESR, erythrocyte sedimentation rate; SSZ, sulfasalazine; WOMAC, Western Ontario and MacMaster Universities Osteoarthritis Index.

for both groups). We found no other major differences between groups in patients with and without peripheral arthritis.

Figure 1 shows the details of patients completing the 24-week study period: 79 (71%) treated with SSZ and 88 (75%) with placebo. In all, 17 patients receiving SSZ withdrew owing to adverse events, including gastrointestinal symptoms (n = 5), infections (n = 2), and allergic reaction, leucopenia, rash, aesthenia, deafness, arthropathy, recurrent iritis, back pain, depression and for abnormal (non-serious) liver function tests (n = 1 each). In the placebo group, 17 patients withdrew because of adverse events, including headache (n = 2), sleep disorder (n = 1), pruritis or urticaria (n = 4), allergic reaction (n = 1), infection (n = 1), gastrointestinal symptoms (n = 5), arthropathy (n = 2) and gastrointestinal haemorrhage (n = 1).

Efficacy

The primary outcome for the study was the mean BASDAI, which dropped considerably to 3.7 (2.7) in the SSZ group at the end of the 24-week study and to 3.8 (2.4) in the placebo group (table 2, fig 2).

We found no major difference in treatment effect between the groups (fig 2). Also, treatment groups did not differ significantly for any of the individual items of the BASDAI (data not shown), or for BASFI, WOMAC Index, CRP, ESR, morning stiffness, chest mobility or anterior spinal flexion (table 2). However, after 3 months of treatment, the median dose of NSAIDs was markedly lower in the SSZ group than in the placebo group (28 mg *v* 88 mg diclofenac or equivalent/day).

When subgroups were analysed for the presence or absence of peripheral arthritis at baseline (retrospective analysis), patients with IBP but no peripheral arthritis treated with SSZ benefited significantly (p = 0.03; mean (SD) BASDAI fell from 5.1 (1.3) to 2.8 (2.3)) compared with those treated with placebo (from 5.2 (1.6) to 3.8 (2.4); fig 3). Spinal pain (improvement of 2.9 (2.9) with SSZ *v* 1.7 (3.0) with placebo; p = 0.03) and overall level of morning stiffness (improvement of 2.8 (2.6) with SSZ *v* 1.7 (3.0) with placebo; p = 0.05) were found to improve significantly with treatment; all other individual BASDAI items improved but did not reach significance. We found no significant difference in the BASDAI or in any of the individual BASDAI items between treatment groups in the subgroup of patients with IBP and peripheral arthritis. Inflammatory markers did not show a reduction with treatment in either subgroup (p>0.25). Retrospective analysis of patients with purely axial symptoms and HLA B27 did not show a significant effect of treatment with SSZ on the BASDAI (p = 0.12); however, patient numbers were small.

Safety

A similar number of adverse events were noted in each arm, with 83% of patients in each group reporting an adverse event (table 3). Most adverse events were mild and did not require discontinuation of the drug. Six patients receiving SSZ and 10 receiving placebo reported serious adverse events. Adverse events that were reported in at least 5% of patients in either group occurred at similar rates in the SSZ and the placebo groups, with the exception of aesthenia, which was reported by 15 (13.4%) patients treated with SSZ compared with 5 (4.2%) given placebo (p = 0.03). Gastrointestinal symptoms including nausea, vomiting, abdominal pain and diarrhoea were not significantly different between treatment groups

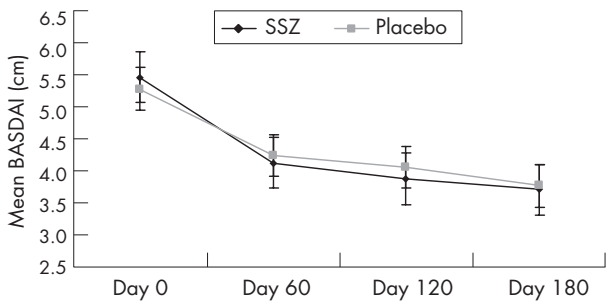

Figure 2 Mean Bath Ankylosing Spondylitis Disease Activity Index (BASDAI; cm) in patients receiving sulfasalazine (SSZ) and placebo.

Table 3 Incidence of adverse events

	SSZ (n=112)	Placebo (n=118)
Any adverse event	93 (83.0)	98 (83.1)
Serious adverse event	6 (5.4)	10 (8.5)
Fatal serious adverse event	0 (0.0)	0 (0.0)
Adverse events possibly related to drug under study	64 (57.1)	52 (44.1)
Adverse events occurring in ⩾5% of patients in either treatment group		
Headache	19 (17.0)	17 (14.4)
Nausea	17 (15.2)	11 (9.3)
Abdominal pain	16 (14.3)	16 (13.6)
Rhinitis	15 (13.4)	18 (15.3)
Aesthenia	15 (13.4)*	5 (4.2)
Diarrhoea	10 (8.9)	15 (12.7)
Vertigo	10 (8.9)	3 (2.5)
Back pain	9 (8.0)	5 (4.2)
Vomiting	9 (8.0)	4 (3.4)
Arthralgia	8 (7.1)	8 (6.8)
Pain	8 (7.1)	7 (5.9)
Rash	8 (7.1)	6 (5.1)
Bronchitis	7 (6.3)	9 (7.6)
Pruritis	6 (5.4)	12 (10.2)
Pharyngitis	6 (5.4)	10 (8.5)

SSZ, sulfasalazine.
Values are n (%).
*Significantly higher than in the placebo arm ($p<0.05$).

(all $p>0.2$). No clinically relevant laboratory abnormalities were reported in either group; in particular, no cases of raised levels of hepatic enzyme or blood dyscrasia were found.

DISCUSSION

This is the first study to be carried out on the use of DMARDs in patients with uSpA and early ankylosing spondylitis, with IBP being the leading clinical symptom. Both SSZ and placebo improved signs and symptoms of patients with uSpA and early ankylosing spondylitis. When the complete population was analysed together, logistic regression did not show any marked differences between the groups at 24 weeks. However, subgroup analysis showed that SSZ may well have an important effect on IBP in patients without peripheral joint disease, which has not been previously examined in the literature.[12]

The efficacy of SSZ for axial symptoms in uSpA is particularly interesting, as recent studies on patients with ankylosing spondylitis who fulfil the modified New York criteria have failed to show an effect of SSZ on IBP alone. In a study of 85 patients with ankylosing spondylitis with relatively short disease duration, who are more likely to resemble our study population, no major difference was seen between patients treated with SSZ and those receiving placebo in spinal pain, although the SSZ group reported less morning stiffness after 26 weeks of treatment, and inflammatory markers were seen to fall significantly.[13] An earlier randomised controlled trial on patients with an average of 10 years of ankylosing spondylitis without peripheral joint disease found that considerably more patients reported treatment with SSZ to be more effective than placebo; however, for most variables measured (including pain, spinal mobility and joint index) both SSZ and placebo groups improved and so significant differences between groups could not be shown.[14] Clegg *et al*[5] showed that SSZ was effective for peripheral arthritis in 619 patients with ankylosing spondylitis, psoriatic arthritis and reactive arthritis, but was not markedly different from placebo in the subset of patients with predominantly axial disease, possibly attributable to the longer, more advanced disease in the patients with ankylosing spondylitis. SSZ has also been shown to reduce the recurrence of ankylosing spondylitis-related anterior uveitis over 3 years.[15] This was not an outcome parameter in our study. Recently published recommendations for the management of ankylosing spondylitis suggest that SSZ may be considered in patients with peripheral arthritis, but that there is no evidence for its use in axial disease.[16 17]

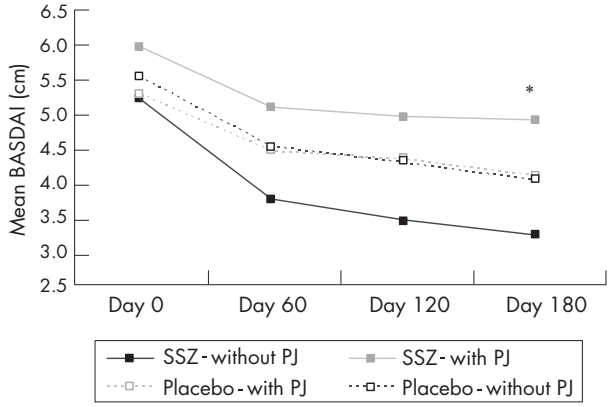

Figure 3 Mean Bath Ankylosing Spondylitis Disease Activity Index (BASDAI; cm) in patients treated with sulfasalazine (SSZ) and placebo, according to the presence or absence of peripheral joint inflammation. *Mean change significantly different between SSZ and placebo, in the subgroup without peripheral joint involvement (PJ), $p=0.02$.

Clearly, effective, inexpensive DMARD treatment is needed for early SpA symptoms in patients who do not qualify for tumour necrosis factor α inhibitors but whose condition may well progress to full ankylosing spondylitis disease with its concomitant functional and structural morbidity. Current recommendations for the use of tumour necrosis factor α inhibitors in ankylosing spondylitis require a definitive diagnosis of ankylosing spondylitis according to accepted criteria, active and refractory disease, and failure of treatment with SSZ in patients with predominantly peripheral arthritis.[18] Open studies on treatment with antitumour necrosis factor-α in patients with severe, active uSpA have shown a marked benefit on the BASDAI, BASFI, spinal pain, peripheral arthritis and quality of life with etanercept[19] and with infliximab.[20] Nevertheless, it is neither clinically meaningful on the basis of what we know now nor probably cost effective to treat all of these patients with tumour necrosis factor α blockers at an early stage of disease, leaving a therapeutic window for DMARDs such as SSZ.

Interpretation of the study results is difficult for several reasons. Firstly, the BASDAI may not have been the appropriate primary outcome measure in this population. Although the use of the BASDAI as an outcome measure is well validated in ankylosing spondylitis,[21 22] it has not been evaluated in patients with uSpA with IBP as the primary symptom. A composite index of patient-reported fatigue, axial pain, peripheral joint and entheseal involvement and morning stiffness, the BASDAI has been shown to be higher in patients with ankylosing spondylitis with involvement of peripheral joints,[23] due partly to a disproportionate contribution of the question on peripheral joints to the overall BASDAI score. Bearing this in mind, we believe that the BASDAI is probably not as sensitive to change in pure axial symptoms. Despite this, the individual axial symptoms of spinal pain and morning stiffness improved markedly with treatment only in the subgroup of patients whose peripheral joints were not affected, suggesting that this may be a real effect and not a result of inherent problems with the BASDAI itself as an outcome measure. Retrospective analysis of patients who are more likely to have early axial ankylosing spondylitis (pure axial symptoms and HLA B27), however, did not show an effect of the treatment; it is difficult to draw

any conclusions based on this observation owing to small patient numbers. At the time this study was designed, the Assessment in Ankylosing Spondylitis response criteria[24] had not been formally developed and as such all of the required features were not measured in this study. It would be interesting to see the effect of SSZ on response rates in our population, as the Assessment in Ankylosing Spondylitis response criteria do not include peripheral joint measures.

Secondly, the dosage of NSAIDs permitted was not standardised, with patients allowed to decrease their regular dosage over the 26-week study period. This may have obscured a real treatment effect (type II error), in that patients treated with SSZ were taking considerably less NSAIDs at the end of the study than the placebo group, and it has been shown recently that small differences in the NSAID dose can strongly influence the clinical outcomes in ankylosing spondylitis.[25] It was considered unethical to force patients to take the same NSAID dose over a long time when they have no clinical symptoms, as there is no evidence that this is more beneficial. Therefore, dose reduction was permitted in the study protocol. In general, our patients are keen to reduce their NSAIDs when possible and, although one recent study has shown reduced radiological progression with continuous NSAID use (as opposed to on-demand use),[26] it is not straightforward to require continuous treatment in the light of the well-recognised gastrointestinal and potential cardiovascular toxicity associated with these drugs.

Thirdly, the small percentage of radiographs available does not permit the exclusion of patients who may have more advanced ankylosing spondylitis. Extrapolation of the available radiographic data suggests that the number of patients with formal ankylosing spondylitis and spinal syndesmophytes is low. SSZ is ineffective for spinal disease in patients with longstanding ankylosing spondylitis,[5] and thus the presence of such (unrecognised) patients with ankylosing spondylitis in our population would bias the results towards the null—that is, would lessen any true treatment effect that may be detected. Nevertheless, the lack of radiographic data for all participants affects the interpretation and generalisability of the study.

Finally, there are no formal diagnostic criteria for diagnosing uSpA; the concept was formalised as a part of the ESSG classification criteria for spondyloarthritides, primarily for use in epidemiological studies and clinical trials. However, the proportion of HLA B27-positive patients in this study was consistent with that seen in the initial ESSG population, and 50% of study patients had raised levels of CRP, more consistent with the population with ankylosing spondylitis. The mean age of the patients in our trial was somewhat higher than we would expect in a trial with patients with SpA who are prone to developing ankylosing spondylitis, as the mean age at onset of ankylosing spondylitis is 26 years.[27] Furthermore, a predominance in men would be expected. The likely explanation for the older age of the cohort is the natural history of the SpA subgroup under study; 40–50% of patients with SpA will never progress to ankylosing spondylitis, but will remain in the ''undifferentiated'' category.[3] Late onset of disease is also more frequent in a subset of patients with uSpA than in those with ankylosing spondylitis, and has a more equal distribution by sex,[28] as seen in our cohort. IBP is not a strong predictor for SpA; with ankylosing spondylitis as the gold standard, IBP has a sensitivity and specificity of about 70% for diagnosing SpA,[29] and additional criteria, such as objective inflammation on a magnetic resonance scan, are required. This makes the interpretation of our results more complicated, although our population was intended to be a cohort with IBP and not solely an early ankylosing spondylitis group.

Therapeutic options are required for patients with IBP and uSpA, to relieve symptoms and to prevent potential disease progression to ankylosing spondylitis and concomitant functional disability. SSZ has for the first time been shown to be effective for axial symptoms in the subgroup of patients without peripheral arthritis and warrants further investigation in this setting.

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Funding: This study was sponsored by Pfizer GmbH, Karlsruhe, Germany (originally Pharmacia & Upjohn), who provided the study drug and financial support.

Competing interests: None.

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